ORIGINAL ARTICLE

Selected Prognostic Factors of Malignant Uveal Melanoma

Svetlošáková Z.[1], Krásnik V.[1], Gergišáková H.[2], Babál P.[2], Kusenda P.[1]

[1]Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava
Head: doc. MUDr. Vladimír Krásnik, PhD.

[2]Institute of Pathological Anatomy, Faculty of Medicine, Comenius University in Bratislava
Head: prof. MUDr. Ľudovít Danihel, PhD.

First author:
MUDr. Zuzana Svetlošáková
Záporožská 6
851 01 Bratislava
e-mail: zuzana.svetlosakova@gmail.com

SUMMARY

Selected Prognostic Factors of Malignant Uveal Melanoma

Malignant uveal melanoma is the most common intraocular tumor in adults. Despite very good local treatment results, patients` survival has not improved in the last decades. The main cause of death is metastatic spread, which occurs with a variable time delay after tumor discovery in 50 % of patients. After metastasis development the mean survival rate decreases to less than 6 months. Progression to metastatic disease is associated with different prognostic factors. The spectrum of conventional clinical and histopathologic prognostic factors like age, tumor size, location, extrascleral growth, histopathologic cell type, vascularisation, invasion of sclera, etc., has been enlarged by using new immunological, molecular, immunohistochemical and cytogenetical methods. Current research also focuses on development of an adjuvant systemic therapy which could delay or prevent metastasis development in high-risk patients. It is necessary to determine reliable prognostic factors in order to select potential candidates for such a systemic treatment. In this article we present a short overview of known prognostic factors of uveal melanoma.

Key words: malignant uveal melanoma, metastasis, prognostic factors

Čes. a slov. Oftal., 68, 2012, No. 1, p. 38–42

INTRODUCTION

Malignant uveal melanoma (MUM) is the most frequently occurring primary intraocular tumour in adults. It may be localised in the iris (6-9%), in the ciliary muscle (9-16%) and most frequently in the choroid (75-85%) (18).The average age-standardised incidence of MUM in a heterogeneous population such as the USA is 5.1 per 1 million (37). The highest incidence was recorded in the age group 60 to 64 years (35). A higher incidence of MUM has been recorded in men and white patients, who constitute more than 90% of cases of MUM (35).

TREATMENT

The possibilities of current treatment of MUM can be divided into bulbus preserving (observation with photograph of fundus, photocoagulation, laser coagulation, thermotherapy, radiotherapy, microsurgical resection) and radical procedures (enucleation of bulb, exenteration of eye socket) (14, 20). The trend in current treatment of MUM is to anticipate the development of metastatic disease, whilst preserving a cosmetically acceptable eye with functioning vision. The choice of treatment is individual and reflects the local finding (locality, size, character of tumour), as well as the overall condition of the patient (19). Despite very good results of local treatment of MUM, at present we are not able to prevent the development of fatal metastatic disease by current methods. Malignant uveal melanoma and its metastases are resistant to systematic treatment, and the results of chemotherapy and immunotherapy to date are unsatisfactory. Since no prospective randomised study comparing the effectiveness of various types of treatment of MUM metastases has been conducted to date (surgical excision, chemotherapy applied to the arteria hepatica, transarterial embolisation, immunoembolisation, isolated hepatic perfusion and percutaneous hepatic perfusion), selection of therapy of metastatic MUM depends on the availability of therapeutic modalities and the experiences of the individual workplaces (31).

PROGNOSIS

Despite very good results of localised treatment of MUM, in the last decade there has not been any significant change in the length of survival of patients with this disease (36). Metastatic dispersion is the main cause of death in patients with MUM. Metastases develop at various time intervals from the determination of diagnosis in up to 50% of patients, and depend on the presence of a number of prognostic factors. The cumulative occurrence of metastases was within the range of 25% at an interval of 5 years from treatment, and on the level of 34% at an interval of 10 years from treatment in the study by the Collaborative Ocular Melanoma Study Group (COMS) (9). Malignant uveal melanoma metastasises exclusively via a hematogenic pathway, since the uvea does not contain lymphatic vessels. The most frequent locations of occurrence of metastases are the liver (90%), the lungs (24%), bones (16%), in rare cases the skin, subcutis and CNS (8, 23). The anatomical locality of the metastases substantially influences the length of the patient's survival. Extra-hepatic occurrence of metastases is linked to significantly longer survival (median 19-28 months) (4). In the majority of cases, however, metastases occur precisely in the liver, which results in survival of 1 year in only approximately 10-15% of patients (4). Local progression of the tumour process into the eye socket following enucleation or radiotherapy is very rare (16).

The attempt to identify the cause of the development of metastases which cannot be influenced by local treatment of the primary ocular tumour has been the subject of several works. At present, however, many experts concur in the opinion that the origin of metastases is conditioned by micro-metastases present before the commencement of local treatment. These metastases remain hidden for a longer period, until they develop into a detectable form of metastatic disease (12). In the light of these findings, current research focuses on the development of adjuvant systematic treatment, which could detect or prevent the progression of micro-metastases into an untreatable macro-metastatic form of disease, especially in patients in whom the presence of such micro-metastases is highly probable. The identification of these "risk" patients requires determination of reliable prognostic factors.

PROGNOSTIC FACTORS

Clinical prognostic factors

During the course of the last decades, several authors have referred to the fact that MUMs of larger dimensions have a higher probability of developing metastases than small MUMs. Tumours of the corpus ciliare and choroid are differentiated on the basis of the regulations of the 7th edition of the TNM classification of the American Joint Committee on Cancer (AJCC) from 2010 (10). The stage of the individual categories of T, N and M is determined on the basis of clinical symptoms with applicable supplementing by further examinations (table 1).

In addition to size, the prognosis is also influenced by the shape of the tumour (fig. 1). Diffuse forms of growth of MUM are considered to be more aggressive, and in the case of MM of the iris and corpus ciliare, ring growth of the tumour is also considered aggressive.

The anatomical locality of MUM also links to the prognosis of the disease. Malignant melanoma of the iris has a better prognosis in comparison with MM of the corpus ciliare and MM of the choroid (17). One of the causes is probably the smaller size at the time of diagnosis. However, it seems that MM of the iris also has lower metastatic potential. In their sample of 1043 patients, Geisse and Robertson (21) described the occurrence of metastases at the level of 3-5% over a 10-year observation period. In the interpretation of these results, however, it is necessary to exercise caution, since MM of the iris is a rare disease, and in several studies the patients have dropped out of the observation (21). The Danish authors recorded death caused by metastases in 10% of patients in a sample of 81 patients, without losing any of the observed patients (26). Several authors have recorded longer survival of patients with nodular MM of the iris in comparison with patients with diffuse MM penetrating into the stroma of the iris (33).

Table 1. TNM classification of MUM of ciliary muscle and choroid (part "T") according to AJCC. According to Edge et al. 2010

Thickness of tumour (mm)							
>15.0	4	4	4	4	4	4	4
12.1-15.0	3	3	3	3	3	4	4
9.1-12.0	3	3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1-6.0	6.1-9.0	9,1-12.0	12.1-15.0	15.1-18.0	>18.0
Largest diameter of base of tumour (mm)							

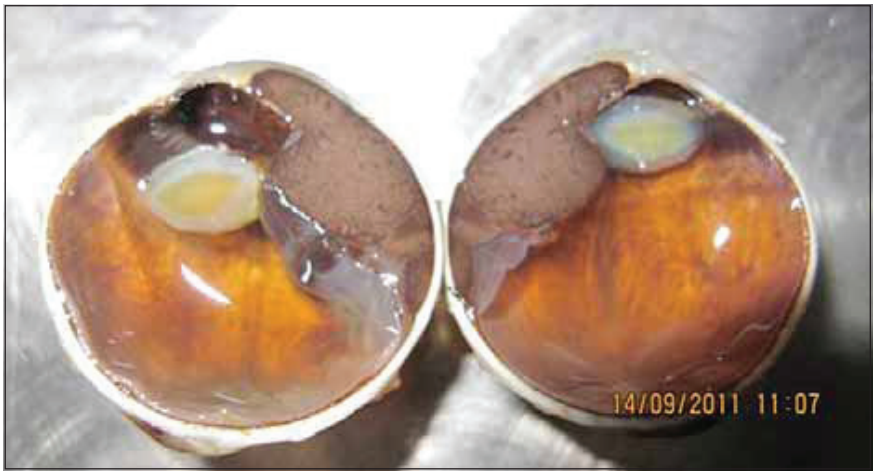

Fig. 1. Malignant melanoma of corpus ciliare in stage T3N0M0 with subluxation of lens and overgrowth into anterior ocular chamber

Further clinical prognostic factors may include infiltration of emissaries of the sclera, extrascleral spread, edge of the tumour projecting in front of the equator of the eyeball, more advanced age of patient, male sex and neovascular glaucoma.

Histopathological and cytomorphological prognostic factors

Cytological and histophatholocial classification of MUM, reflecting prognosis, was originally proposed by Callender et al. (6). This classification differentiates between two fundamental cell types of MUM (pivotal and epetheloid), and is currently the basis of accepted cytological classification of MUM according to the WHO (7). The epitheloid cell type of MUM is distinguished by its more aggressive character and increased risk of development of metastases. Other adverse prognostic factors include extrascleral spread of the tumour and infiltration of the emissaries of the sclera.

Folberg et al. (13) recorded the significance of the type of vascularisation of the tumour as a prognostic factor of MUM. A new formation of capillaries is partially a response to a tumour on the part of the host, and on the other hand also an inevitable step in the process of the haematological spread of metastases. By using colouring of histological cross-sections by the PAS (periodic acid-Schiff) method, they compiled a classification with 9 types of vascularisation, which was later simplified by McLean et al. (28) into three categories, according to the presence of circuits, in which circuits may be present, absent or inconclusively present. A

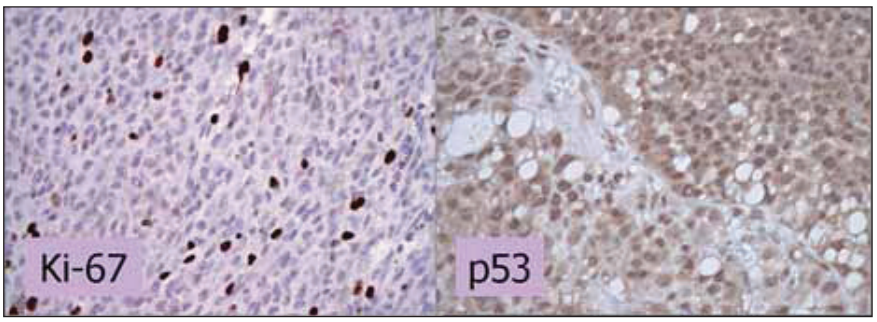

Fig. 2. Immunohistochemical examination of expression Ki-67 and p53. Examination of expression Ki-67 documents proliferative activity of MUM. In the histological preparation less than 10% of nuclei are positive, which means a favourable prognosis. In the case of p53 the colouring of the nuclei in 85% represents increased expression of p53 and testifies to a less favourable prognosis. Enlarged 400x.

positive finding of capillary circuits or capillary networks anywhere within the tissue cross-section represents an unfavourable prognostic factor. In 1999, Maniotis et al. (27) described a new process of formation of a capillary bed in the case of human melanoma, both in vitro and in vivo. They named this process "vasculogenic mimicry", and at present this is considered one of the markers of aggressive behaviour of primary and metastatic melanomas. "Vasculogenic mimicry" represents a microcirculatory bed remaining from the extracellular matrix, delimited by cancer cells without the presence of endothelial cells.

Proliferation of cancer cells of malignant uveal melanoma

Several studies have confirmed that the determination of the number of cell mitoses, indication of DNA synthesis (determination of fraction of S-phase DNA) through the help of flow cytometry and change of organisational areas of the nucleus have a significant relationship to the prognosis of MUM.

Immunohistochemistry is a more precise method of evaluating proliferative activity in comparison with the determination of fraction of S--phase. Proliferation markers include Ki-67 and PCNA, which in the case of MUM are linked to death as a result of metastases (32). The nuclear antigen Ki-67 is exprimated during the active phases of the cellular cycle and is not detectable during the calm cell phase (fig. 2). Factors linked to positivity of Ki-67 include expression of p53, large dimensions of tumour, epitheloid cell type, certain types of vascularisation and shorter survival (2).

Cell surface receptors

Cell surface receptors, which mediate intercellular connections, as well as the connection of the cell and the matrix, play an important role in the metastatic process. Beutel et al. (5) examined immunohistochemical detection of the expression of the Melanoma Cell Adhesion Molecule (MCAM), and pointed to its importance as a potential marker of metastasising MUM. The blockade or inhibition of this molecule can be applied in future in the treatment or prevention of the occurrence of MUM metastases. A similar linkage to adverse prognosis was also described by the authors Anastassiou et al. (3) in the case of the Intercellular Cell Adhesion Molecule-1 (ICAM-1).

Immunological prognostic factors

The theory of immunological control, according to which cancer cells exprimate new antigens distinguished and eliminated by the immune system, was presented 30 years ago. Unique anatomical, physiological and immunoregulatory mechanisms of the eye however prevent the induction and expression of the immune response due to the phenomenon known as "immunity privilege". The presence of a tumour of the infiltrating lymphocytes (TIL) and a tumour of the infiltrating macrophages (TIM), in contrast with MM of the skin, is linked to a less favourable prognosis and points to the fact that the immune response need not necessarily eliminate the tumour, but may conversely support its development (41).

Genetic abnormalities

Advances in the field of genetic research have enabled the discovery of new prognostic factors on the level of chromosomes, genes, proteins or signal pathways.

Chromosome abnormalities

One of the first and at the same time most important chromosome abnormalities determined in MUM is monosomy 3, loss of one of two copies of the 3rd chromosome. Monosomy 3 is linked to the development of metastases and is found in approximately 50% of cases of MUM (34). The presence of this defect reduces five-year survival by approximately 50% and is linked to further prognostically unfavourable factors: epitheloid cell type, presence of extravascular matrix, larger diameter of tumour, occurrence in the area of the corpus ciliare (34). By contrast, the presence of disomy of the 3rd chromosome is linked to a favourable prognosis. However, for the meantime it has not been clarified as to whether monosomy 3 contributes causally to the progression of the melanoma by the division of a specific gene or genes, or whether it is simply a marker of genome instability, which accompanies the progression of the tumour. At present, after determination of the profiles of gene expression, monosomy of chromosome 3 ranks amongst the most reliable predictors of the incidence of metastases.

Excess copies of the chromosome 6p have been found in approximately one quarter of MUMs. In contrast with monosomy 3, the presence of the isochromosome 6p is linked to a more favourable prognosis, and these abnormalities very rarely occur concurrently. Within the framework of abnormalities of chromosome 6, some authors have also described a loss of the copy of chromosome 6q, which on the contrary is linked to a metastasising tumour. However, this connection is less significant in the case of changes of chromosomes 3 and 8 (22).

The presence of abnormalities of chromosome 8 has been determined in more than 40% of MUMs (29). The prognostic significance is similar as in the case of monosomy 3 and is linked to a higher risk of the occurrence of metastases, larger dimensions of the tumour and more aggressive histological type (38).

Of other, less frequent chromosome abnormalities of MUM, changes of chromosomes 1, 9, 13 and 21 have been described (1).

In future, genetic examination shall probably also influence therapy of primary MUM. If the hypotheses about the non-metastatic character of MUM with disomy of chromosome 3 are confirmed, it would be unnecessary to

treat asymptomatic tumours with preservation of visual functions. However, patients with a high risk of metastasising MUM would also not need to consent to enucleation and the sacrifice of still useful vision in a situation in which there was vain hope of improvement of their chances of survival (15).

Alteration of genes, proteins and signal pathways in connection with malignant cellular transformation

The above described alterations of chromosomes point to the fact that the progression of MUM is linked to specific disorders on the molecular level. In the literature, amplification of the oncogene c-Myc, increased expression of the proto-oncogene HDM2 (human homologue of murine double minute 2) and changes in the signal pathways Rb, Bcl-2, TGF-β and MAPK are linked to a higher risk of incidence of metastases.

One of the damaged molecules in MUM appears to be the protein p53, the main role of which is protection against cancerous transformation of the cell. In more than one half of human tumours, mutation of coding gene p53 has been determined (fig. 2). To date, references have been made to the connection of p53 to extraocular spread of the tumour and invasion into the capillaries, increased proliferative activity and epitheloid cellular type (24). Increased expression of p53 has been determined in cases of MUM treated by radiotherapy as a response to radiation damage to cells (25). However, in their work Erol et al. (11) described increased expression of p53 only in the case of 2 of a total number of 15 tumours, and similar results were published by Tokošová et al. (39), where there was increased expression in only 4 out of 28 tumours. For this reason, neither the position of p53 as a prognostic factor and its role in influencing radiosensitivity of MUM have been unequivocally defined as yet.

Profiles of gene expression

Although the alteration of chromosomes 3, 6 and 8q are linked to death caused by metastases, the clinical utilisation of these observations has not yet been precisely stipulated. In addition, we still do not know the answer to the question as to whether the aforementioned chromosome changes are linked to a deregulation of specific genes, or if they are merely markers of the progression of the tumour. In an endeavour to reveal the biological basis of the incidence of metastases, Onken et al. (29) divided primary MUM into two groups on the basis of profiles of gene expression. Malignant uveal melanomas belonging to the first group of tumours metastasise very rarely, whilst MUM belonging to the second group demonstrate frequent incidence of metastases (29, 40, 42). Within the framework of the second group, there is a very frequent finding of monosomy of the third chromosome. Although monosomy 3 is not such a precise predictor of metastases as the profile of gene expression, the relationship of the second group and monosomy 3 indicates that monosomy 3 may be responsible for the global change of the gene expression of the second group of tumours (30, 40, 42). The subject of a prospective study being conducted by COMS at present is the comparison of the predictive values of both prognostic factors, namely abnormalities of chromosome 3 and profiles of the gene expression of MUM. In the future COMS is planning a multicentric clinical study focusing on systematic adjuvant treatment of high risk patients (belonging to the second group according to the profile of gene expression). The relationship between the individual profiles of gene expression and the incidence of metastases continues to remain the subject of intensive scientific research.

CONCLUSION

Malignant uveal melanoma represents a serious, hitherto still insufficiently researched problem of ophthalmology. More precise determination of prognosis or detection of new potential goals of treatment would represent a great benefit in the management of patients with this disease.

Supported by grant of Comenius University no. UK/204/2011.

LITERATURE

1. Aalto, Y., Eriksson, L., Seregard, S. et al.: Concomitant loss of chromosome 3 and whole arm losses and gains of chromosome 1, 6, or 8 in metastasizing primary uveal melanoma, Invest Ophthalmol Vis Sci, 42, 2001, 2: 313–7.
2. Al-Jamal, R.T., Kivela, T.: KI-67 immunopositivity in choroidal and ciliary body melanoma with respect to nucleolar diameter and other prognostic factors, Curr Eye Res, 31, 2006, 1: 57–67.
3. Anastassiou, G., Schilling, H., Stang, A. et al.: Expression of the cell adhesion molecules ICAM-1, VCAM-1 and NCAM in uveal melanoma: a clinicopathological study, Oncology, 58, 2000, 1: 83–8.
4. Bedikian, A.Y.: Metastatic uveal melanoma therapy: current options, Int Ophthalmol Clin, 46, 2006, 1: 151–66.
5. Beutel, J.,Wegner, J.,Wegner, R. et al.: Possible implications of MCAM expression in metastasis and nonmetastatic of primary uveal melanoma patients, Curr Eye Res, 34, 2009, 11: 1004–9.
6. Callender, G.R.: Malignant melanotic tumors of the eye: a study of histologic types in 111 cases, Trans Am Acad Ophthalmol Otolaryngol, 36, 1931, 131-42.
7. Campbell, R.J., Sobin, L.H.: WHOHistological typing of tumours of the eye and its adnexa, New York, Springer, 1998, 115s.
8. Diener-West, M., Reynolds, S.M., Agugliaro, D.J. et al.: Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23, J Clin Oncol, 22, 2004, 12: 2438–44.
9. Diener-West, M., Reynolds, S.M., Agugliaro, D.J. et al.: Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26, Arch Ophthalmol, 123, 2005, 12: 1639–43.
10. Edge, S.B., Byrd, D.R., Compton, C.C. et al.: AJCC Cancer Staging Handbook, New York, Springer, 2010, 730 s.
11. Erol, N., Oner, U., Artan, S. et al.: Chromosomal abnormalities, p53 and Bcl-2 expression and clinical outcome in choroidal melanoma, Melanoma Res, 14, 2004, 6: 473–8.
12. Eskelin, S., Pyrhonen, S., Summanen, P. et al.: Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment, Ophthalmology, 107, 2000, 8: 1443–9.

13. Folberg, R., Pe'er, J., Gruman, L.M. et al.: The morphologic characteristics of tumor blood vessels as a marker of tumor progression in primary human uveal melanoma: a matched casecontrol study, Hum Pathol, 23, 1992, 11: 1298–305.
14. Furdová, A.: Nové trendy v liečbe malígneho melanómu uvey. In Rozsíval, P. (Ed), Trendy soudobé oftalmologie, svazek 4, Galén, 2007, s.13–35.
15. Furdová, A., Böhmer, D., Blaško, M. et al.: Genetika uveálnych melanómov (monozómia 3) – porovnanie karyotypu z buniek nádoru, limbálnych kmeňových buniek a periférnej krvi (prvé výsledky). In (Ed), 6. bilaterálne slovensko-české oftalmologické sympózium – Zborník Bratislava, Slovenská oftalmologická spoločnosť, 2011, s. 26–27.
16. Furdová, A., Chynoranský, M., Krajčová, P.: Orbital melanoma, Bratisl Lek Listy, 112, 2011, 8: 466–8.
17. Furdová, A., Oláh, Z.: Malígny melanóm v uveálnom trakte, Bratislava, Asklepios, 2002, 175 s.
18. Furdová, A., Oláh, Z.: Nádory oka a okolitých štruktúr, Brno, Akademické nakladatelství CERM, 2010, 151 s.
19. Furdová, A., Slezák, P., Chorváth, M. et al.: No differences in outcome between radical surgical treatment (enucleation) and stereotactic radiosurgery in patients with posterior uveal melanoma, Neoplasma, 57, 2010, 4: 377–81.
20. Furdová, A., Strmeň, P., Waczulíková, I. et al.: One-day session LINAC-based stereotactic radiosurgery of posterior uveal melanoma, Eur J Ophthalmol, 2011, Published online: 18/04/2011, DOI 10.5301/EJO.2011.7733.
21. Geisse, L.J., Robertson, D.M.: Iris melanomas, Am J Ophthalmol, 99, 1985, 6: 638-48.
22. Ghazvini, S., Char, D.H., Kroll, S. et al.: Comparative genomic hybridization analysis of archival formalin-fixed paraffin-embedded uveal melanomas, Cancer Genet Cytogenet, 90, 1996, 2: 95–101.
23. Gragoudas, E.S.: Proton beam irradiation of uveal melanomas: the first 30 years. The Weisenfeld Lecture, Invest Ophthalmol Vis Sci, 47, 2006, 11: 4666–73.
24. Hussein, M.R.: The relationships between p53 protein expression and the clinicopathological features in the uveal melanomas, Cancer Biol Ther, 4, 2005, 1: 57–9.
25. Janssen, K., Kuntze, J., Busse, H. et al.: p53 oncoprotein overexpression in choroidal melanoma, Mod Pathol, 9, 1996, 3: 267–72.
26. Jensen, O.A.: Malignant melanoma of the iris. A 25-year analysis of Danish cases, Eur J Ophthalmol, 3, 1993, 4: 181–8.
27. Maniotis, A.J., Folberg, R., Hess, A. et al.: Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry, Am J Pathol, 155, 1999, 3: 739–52.
28. McLean, I.W., Keefe, K.S., Burnier, M.N.: Uveal melanoma. Comparison of the prognostic value of fibrovascular loops, mean of the ten largest nucleoli, cell type, and tumor size, Ophthalmology, 104, 1997, 5: 777–80.
29. Onken, M.D., Worley, L.A., Ehlers, J.P. et al.: Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death, Cancer Res, 64, 2004, 20: 7205–9.
30. Petrausch, U., Martus, P., Tonnies, H. et al.: Significance of gene expression analysis in uveal melanoma in comparison to standard risk factors for risk assessment of subsequent metastases, Eye (Lond), 22, 2008, 8: 997–1007.
31. Sato, T.: Locoregional management of hepatic metastasis from primary uveal melanoma, Semin Oncol, 37, 2010, 2: 127–38.
32. Seregard, S., Oskarsson, M., Spangberg, B.: PC-10 as a predictor of prognosis after antigen retrieval in posterior uveal melanoma, Invest Ophthalmol Vis Sci, 37, 1996, 7: 1451–8.
33. Shields, C.L., Shields, J.A., Materin, M. et al.: Iris melanoma: risk factors for metastasis in 169 consecutive patients, Ophthalmology, 108, 2001, 1: 172–8.
34. Scholes, A.G., Damato, B.E., Nunn, J. et al.: Monosomy 3 in uveal melanoma: correlation with clinical and histologic predictors of survival, Invest Ophthalmol Vis Sci, 44, 2003, 3: 1008–11.
35. Singh, A.D., Topham, A.: Incidence of uveal melanoma in the United States: 1973-1997, Ophthalmology, 110, 2003, 5: 956–61.
36. Singh, A.D., Topham, A.: Survival rates with uveal melanoma in the United States: 1973-1997, Ophthalmology, 110, 2003, 5: 962–5.
37. Singh, A.D.,Turell, M.E.,Topham, A.K.: Uveal melanoma: trends in incidence, treatment, and survival, Ophthalmology, 118, 2011, 9: 1881–5.
38. Sisley, K., Parsons, M.A., Garnham, J. et al.: Association of specific chromosome alterations with tumour phenotype in posterior uveal melanoma, Br J Cancer, 82, 2000, 2: 330–8.
39. Tokošová, E., Hermanová, M., Uhmannová, R. et al.: Immunohistochemical detection of the gene p53 and p21 expression in cells of the malignant melanoma of the uvea, Čes Slov Oftalmol, 64, 2008, 4: 153–6.
40. van Gils, W., Lodder, E.M., Mensink, H.W. et al.: Gene expression profiling in uveal melanoma: two regions on 3p related to prognosis, Invest Ophthalmol Vis Sci, 49, 2008, 10: 4254–62.
41. Whelchel, J.C., Farah, S.E., McLean, I.W. et al.: Immunohistochemistry of infiltrating lymphocytes in uveal malignant melanoma, Invest Ophthalmol Vis Sci, 34, 1993, 8: 2603–6.
42. Worley, L.A., Onken, M.D., Person, E. et al.: Transcriptomic versus chromosomal prognostic markers and clinical outcome in uveal melanoma, Clin Cancer Res, 13, 2007, 5: 1466–71.